REMARKS

Claims 5, 7-9, 26-27, 29, 31, 37, 48-51, 56, 58, 69-70, 72, 74, 76, 78, 108, 110, 117, 127-129, 131-135, 137, 147, 150, and 156-163 are pending in the present application. Claims 56, 110, 135, 137, 147, 150 and 162-163 are withdrawn from consideration.

The Examiner asserted that claims 162 and 163 are directed to non-elected subject matter and, hence, were not considered. Applicants traverse. Applicants respectfully submit that claims 162 and 163 depend from claim 158, and recite methods which include all of the limitations of the product of claim 158. Accordingly, these claims could be considered by the Examiner without undue burden. In the event that the Examiner maintains his position that claims 162 and 163 are directed to non-elected subject matter, Applicants expressly reserve the right to prosecute claims directed to the same or similar subject matter in a divisional application.

Additionally, Applicants note that, in accordance with MPEP 821.04(b), Applicants will be entitled to rejoinder of process claims that depend from and include all the limitations of an allowable product claim.

Applicants have amended claims 5, 26, 29, 117, 127, 158, 159, and 161 to address claim objections described below. No new matter has been added.

Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order in which they appear in the Office Action.

Claim Objections

Claims 29 and 161 are objected to for reciting "linker includes" instead of "linker comprises." Applicants note that the terms "comprises" and "includes" are both open, and thus clearly describe the claimed subject matter. Nevertheless, to expedite prosecution, Applicants have amended the claims to recite "comprises", as suggested by the Examiner. Applicants' amendment does not narrow the scope of the claims.

Claims 26 and 159 are objected to for reciting "protein includes a linker" instead of "protein comprises a linker." Applicants note that the terms "comprises" and "includes" are both open, and thus clearly describe the claimed subject matter. Nevertheless, to expedite prosecution, Applicants

have amended the claims to recite "comprises", as suggested by the Examiner. Applicants' amendment does not narrow the scope of the claims.

The Examiner objects to claim 117 for reciting "selected from among" instead of "selected from the group consisting of." Applicants respectfully traverse. The proteases listed in claim 117 are part of a Markush group. According to MPEP 2173.05(h), materials recited in a Markush group "may be recited in the conventional manner, or alternatively. Nevertheless, to expedite prosecution, Applicants have amended claim 117, as suggested by the Examiner. Applicants' amendment does not narrow the scope of the claim.

The Examiner objects to claim 127 for reciting "an adzyme of claim..." Applicants have amended claim 127 to recite "the adzyme of claim 5." Applicants' amendment does not narrow the scope of the claim.

In view of the foregoing amendments, Applicants request reconsideration and withdrawal of the objections to the claims.

Claim Rejections – 35 U.S.C. § 112, 2nd paragraph

Claims 5, 7-9, 26-27, 29, 31, 37, 48-51, 58, 69-70, 72, 74, 76, 78, 108, 117, 127-129, 131-134, 156-157 (which depend from claim 5), 158 and 159-161 (which depend from claim 158) were rejected under 35 U.S.C. 112, second paragraph, as being indefinite.

Claims 5 and 158 were rejected due to recitation of "address site." The Examiner asserts that recitation of the phrase "address site" in claims 5 and 158 is unclear. Applicants traverse. The term "address site" and the use of this term is well-characterized throughout the specification, for example, in paragraphs [0095] and [0182]:

> [0095] The targeting moiety (or "address") is a moiety capable of recognizing and reversibly binding to a pre-determined "address binding site" (also herein "address site"), such as, for example, a soluble or membrane-bound biomolecules, or a component of a biomolecular accretion (e.g., a plaque or other insoluble protein-containing aggregate).
>
> [0182] It will be appreciated that a wide range of entities can be used as targeting moieties in the subject adzymes. Fundamentally, the targeting moiety reversibly binds to a pre-determined feature ("address site") associated with the targeted substrate. The targeting moiety presents one or more surfaces having chemical characteristics (e.g., hydrophobic, steric and/or ionic) which permit it to bind selectively, or relatively selectively, with the address site. In many embodiments, the address will be a modular protein (including peptide) domain which is provided in association with the

> catalytic domain. For example, the targeting moiety can be an antibody, or a fragment of an antibody which retains the ability to bind to the address site. Accordingly, the targeting moiety can be derived from such antibody and antibody fragments as monoclonal antibodies, including Fab and $F(ab)_2$ fragments, single chain antibodies (scFv), diabodies, and even fragments including the variable regions of an antibody heavy or light chain that binds to the address site.

In view of the clear guidance provided in the specification, Applicants assert that the meaning of "address site" is clear and definite. One of skill in the art can readily understand the metes and bounds of the claimed invention. Accordingly, reconsideration and withdrawal of this rejection are requested.

Claims 5, 7-9, 26-27, 29, 31, 37, 48-51, 58, 69-70, 72, 74, 76, 78, 108, 117, 127-129, 131-134, and 156-157 are rejected due to recitation of the phrase "antibody or a functional fragment thereof." Applicants traverse the rejection. A functional fragment of an antibody is well-understood in the art to describe the fragment that is sufficient for carrying out the relevant function of the antibody. In this context, the functional fragment would, like the antibody, serve as a targeting domain that binds to the substrate. Accordingly, the metes and bounds of the claim are clear to one of skill in the art. Nevertheless, to expedite prosecution, Applicants have amended the claims to more particularly point out that the functional fragment is an "antigen binding fragment thereof". Applicants' amendment is not in acquiescence to the rejection, and Applicants reserve the right to prosecute claims of similar or differing scope. Reconsideration and withdrawal of this rejection is requested.

Claims 27 and 160 are rejected due to recitation of the phrase "unstructured peptide." Applicants traverse. The phrase is commonly used in the scientific literature to refer to peptides that have not folded into specific structures. In the specification, a linker that is an unstructured peptide is differentiated from a linker that includes one or more repeats of Ser_4Gly or $SerGly_4$, and a linker that is selected to provide steric geometry between a catalytic domain and a targeting moiety (for example, see paragraph [0038]). Taken in light of the art-recognized use of the term and the teachings provided in the specification, the claim clearly sets forth the metes and bounds of the desired patent protection in a manner that is clear to one of skill in the art. Accordingly, reconsideration and withdrawal of this rejection are requested.

Claim 69 is rejected due to recitation of the phrase "resistant," and claim 157 is rejected as being indefinite because of the recitation of the phrase "resistant to autocatalyzed— [*sic*]" According to the Examiner, the term "resistant" is a term of degree, and it is unclear how much cleavage is required for the adzyme to be considered "resistant." Applicants note that both claims 69 and 157 recite "resistant to autocatalysis" and respectfully traverse the rejection. Paragraphs [0407]-[0417] describe how autocatalysis disrupts the ability of the adzyme to act effectively on its target. These passages provide many embodiments of adzymes that decrease or prevent autoproteolysis. In view of the detailed description provided in the specification and the level and understanding of one of skill in the art, Applicants submit that one of skill can readily appreciate the metes and bounds of the claimed invention. This standard is consistent with that set forth in MPEP 2173.05(b) ("The fact that claim language, including terms of degree, may not be precise, does not automatically render the claim indefinite under 35 U.S.C. 112, second paragraph. *Seattle Box Co., v. Industrial Crating & Packing, Inc.*, 731 F.2d 818, 221 USPQ 568 (Fed. Cir. 1984)"). The MPEP and Federal Circuit support the conclusion that relative terminology is acceptable so long as one of ordinary skill in the art would understand what is claimed, in light of the specification. Such is the case here. Accordingly, reconsideration and withdrawal of these rejections are requested.

Claim 74 is rejected due to recitation of the phrase "adzyme inhibits biological activity of said substrate relative to..." because the Examiner asserts that a substrate could have more than one activity, and a hypothetical adzyme in the prior art may inhibit one but not the other activity. In such a situation, the hypothetical adzyme allegedly might (or might not be) encompassed by claim 74, depending on which biological activity was being considered. Applicants traverse. The claim recites "said adzyme inhibits a biological activity of said substrate relative to said biological activity in the absence of said enzyme" (emphasis added). The claim recites "a biological activity" and does not differentiate between activities. If there exists an adzyme in the literature that affects a biological activity and also possesses all the limitations of claim 5, Applicants respectfully request that the Examiner present such art as part of a rejection under 35 U.S.C. 102 or 103. Such an art-based rejection, and not the instant rejection under 112, second paragraph, would be the appropriate course.

In view of the foregoing arguments, Applicants request withdrawal of the rejections under 35 U.S.C. 112, second paragraph.

Claim Rejections – 35 U.S.C. § 102

Claims 5, 7-9, 37, 48-51, 58, 69-70, 72, 74, 76, 78, 108, 127-129, 156, 157, and 158 were rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Holvoet *et al.* (JBC 1991, vol.266, pp 19717-19724, hereinafter "Holvoet"). The Examiner asserts that a fusion protein disclosed by Holvoet anticipates the pending claims, which recite "a protease domain that cleaves at least one peptide bond of said substrate...and a polypeptide targeting domain that reversibly binds with an address site of said substrate." Allegedly, the fusion protein of Holvoet consists of a urokinase (serine protease) and an anti-fibrin antibody, "wherein the antibody binds fibrin on a blood clot and serine protease of the fusion moiety lyses the blood clot" (emphasis added). Applicants respectfully traverse, and submit that the Examiner has mischaracterized the binding and mechanism of action of the protease disclosed by Holvoet.

It is true that the overall effect of the fusion protein of Holvoet is (1) binding a substrate fibrin through an anti-fibrin antibody and (2) using a protease called urokinase-type plaminogen activator (u-PA) to mediate lysis of the fibrin containing substrate. However, the u-PA does not itself act on the fibrin containing substrate, and therefore is **not** a protease that cleaves the **same** substrate that the anti-fibrin antibody binds. Even when the substrate is broadly construed to refer to a whole blood clot, u-PA still does not cleave the same substrate as that bound by the anti-fibrin antibody.

Holvoet provides an anti-fibrin antibody that binds to fibrin (or more broadly, to a fibrin clot or blood clot) and u-PA which binds to and cleaves plasminogen. Plasminogen is a freely-circulating zymogen, and as such, it is **not** a component of the blood clot (e.g., substrate). Plasminogen is secreted into the blood and circulates in an inactive form until it is cleaved to form plasmin. Plasmin, in turn, cleaves fibrin and other substrates associated with cleavage of blood clots. While it may be true that, in Holvoet, the activity of the fusion protein ultimately and indirectly leads to lysis of the blood clot, it is simply not scientifically accurate to interpret Holvoet as providing a system in which the protease (u-PA) binds to and cleaves the same substrate as that

bound by a targeting domain. This deficiency of Holvoet is true both for embodiments in which the instant claims encompass adzymes where the targeting domain and protease domain act on the very same protein, as well as embodiments in which the instant claims encompass adzymes where the targeting and protease domains act on different proteins associated in the same substrate complex. In either case, Holvoet fails to teach the claimed invention because the u-PA protease of Holvoet does not act on a component of the clot. Rather, the u-PA protease of Holvoet acts on circulating plasminogen to form plasmin. Because the fusion protein of Holvoet requires activation of other proteins outside of the substrate, rather than acting directly on the same substrate that binds the anti-fibrin antibody, Applicants submit that Holvoet fails to anticipate the claimed invention. Applicants respectfully request reconsideration and withdrawal of the rejection.

Claim Rejections – 35 U.S.C. § 103a

As an initial point, Applicants note that the Examiner has not rejected any of claims 5, 7, 8, 9, 37, 48, 49, 50, 58, 72, 74, 76, 108, 127, 128, 129, or 156-158 under 35 U.S.C. 103(a). Accordingly, should the Examiner wish to reject any of the foregoing claims under 103(a) in an Office Action subsequent to the instant Office Action, such a rejection should be made in a non-final action.

Claim 117 remains rejected under 35 U.S.C. § 103(a) as allegedly unpatenable in view of the combined teachings of Holvoet or Bhatia et al. (Intl. J. Cancer 2000, 85, 571-577, hereinafter "Bhatia") in view of Davis et al. (WO 00/64485, hereinafter "Davis"). The Examiner asserts that one of skill would be motivated to make the protein conjugate of Davis comprising chymotrypsin conjugated to an antibody by gene fusion methodology, as taught by Holvoet or Bhatia. Applicants traverse. To establish a prima facie case of obviousness, the Office must demonstrate (1) suggestion or motivation to combine the references, (2) reasonable expectation of success, and (3) consideration of all claim limitations (MPEP 2143). The cited references do not fulfill these requirements. Claim 117 depends from independent claim 5 and, as discussed above, Holvoet does not teach the elements of claim 5. Neither Davis nor Bhatia remedy this deficiency. Davis discloses enzymes, including chymotrypsin, joined by chemical conjugation to a targeting molecule

which may be a chemical ligand or a protein. Bhatia discloses fusion proteins made up of a bacterial enzyme and an antibody to the tumor-specific molecule carcinoembryonic antibody (CEA). Even if all of the elements of the pending claims were found in the references, which Applicants do not concede, there is no motivation to combine Holvoet, Davis and Bhatia. Starting from Holvoet or Bhatia, both the targets and the substrates were specifically selected to mediate fibrinolysis and tumor-specific targeting of a bacterial enzyme, respectively. The exact components of the fusion proteins were developed for the purposes indicated, thus, one would not be motivated to select new ligands, enzymes, or alternative methods for conjugating the proteins as taught by Davis. Conversely, starting from Davis, one would not be motivated to make the chemically-conjugated molecule of Davis as a fusion protein, as the Examiner suggests. Davis specifically teaches the benefits of using chemical conjugation, rather than using fusion proteins. Chemical coupling imparts greater flexibility in the design of the molecules, and further, facilitates the use of targeting domains that may be small organic molecules or other non-protein ligands. Davis enumerates many advantages of using non-protein targeting moieties on page 21, lines 1-12. In summary, Davis specifically teaches the advantages of using only chemical conjugation techniques, but does not lead one of skill to make fusion proteins. In fact, Davis teaches away from making fusion proteins because such fusions (i) would lack the benefits described by Davis for chemical conjugates and (ii) would be unsuitable for use in the context of non-protein targeting moieties. Applicants assert that there is no motivation to combine the fundamentally distinct teachings of Holvoet, Bhatia, and Davis to arrive at the claimed invention. Accordingly, Applicants respectfully request withdrawal of the rejection.

Claims 26, 27, 29 and 31 remain rejected, while claims 159-161 are newly rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Holvoet in view of Guo et al. (Biotech and Bioeng, 2000, 70, 456-463; herein "Guo"). The Examiner asserts that one of skill is motivated to make a fusion protein (as taught by Holvoet) wherein an enzyme is conjugated to an antibody by a $(Gly_4Ser)_3$ linker as taught by Guo. Applicants traverse this rejection. As described in detail above, Holvoet fails to teach or suggest each and every limitation of the claimed invention. Guo describes a fusion protein comprising L-asparaginase (ASNase), a $(Gly_4Ser)_3$ linker, and a protective scFv,

but the disclosure of the linker and the use of a different antibody does not remedy the deficiencies of Holvoet. Accordingly, the combined teachings of the cited references fail to undermine the patentability of the claimed invention for, at least, failing to teach or suggest each and every limitation of the claimed invention. Reconsideration and withdrawal of the rejection are requested.

Claim 51 remains rejected under 35 U.S.C. 103(a) as allegedly unpatentable over Holvoet in view of Debburman *et al.* (PNAS 1997 94, 13938-13943, hereinafter "Deburrman"). The Examiner asserts that it would have been obvious for one of skill to make a fusion protein comprising a protease conjugated to a specific antibody as taught by Holvoet, in order to target prion proteins as taught by Debburman. Applicants traverse.

As described in detail above, Holvoet fails to teach or suggest each and every limitation of the claimed invention. Deburrman does not remedy the deficiencies of Holvoet. Accordingly, the combined teachings of the cited references fail to undermine the patentability of the claimed invention for, at least, failing to teach or suggest each and every limitation of the claimed invention. Reconsideration and withdrawal of the rejection are requested.

Claims 131-134 remain rejected under 35 U.S.C. 103(a) as allegedly unpatentable over Holvoet in view of Sanderson et al. (Medic. Res Rev 1999, 19, 179-197, hereinafter "Sanderson"). The Examiner asserts that one of skill would be motivated to add a reversible protein inhibitor as taught by Sanderson in order to make a pharmaceutical preparation comprising a fusion protein as taught by Holvoet. Applicants traverse.

As described in detail above, Holvoet fails to teach or suggest each and every limitation of the claimed invention. However, the features provided by Sanderson fail to remedy the deficiencies of Holvoet. Accordingly, the combined teachings of the cited references fail to undermine the patentability of the claimed invention for, at least, failing to teach or suggest each and every limitation of the claimed invention. Reconsideration and withdrawal of the rejection and requested.

In conclusion, Applicants contend that the claims are nonobvious in view of the cited references. Accordingly reconsideration and withdrawal of the rejections under 35 U.S.C. § 103(a) are requested.

Double Patenting

Claims 5, 7-9, 26-27, 29, 31, 35, 37, 52-53, 58, 69-70, 72, 74, 76, 78, 108, 119, 127-129, and 131-134 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 1, 4-5, 30-34, and 37-41 of copending Application Nos. 10/792,498 and 10/650,591.

Applicants reiterate that, if conflicting claims are first allowed in these two co-pending U.S. Applications, Applicants note that, pursuant to 37 C.F.R. § 1.130(b), a timely filed terminal disclaimer in compliance with 37 C.F.R. § 1.321(c) may be used to overcome the double patenting rejection. In the meantime, and given that there has been no indication of allowable subject matter in the instant application, Applicants ask that this rejection be held in abeyance until indication of allowable subject matter. Applicants will submit a terminal disclaimer, if necessary, upon indication of allowable subject matter.

Applicants note that, in accordance with MPEP 804.I.B., the Examiner will maintain the provisional double patenting rejection until there are either no longer any conflicting claims or the double patenting rejection is the only remaining rejection in at least one of the applications.

Co-Pending Applications

The following co-pending, commonly assigned applications are brought to the Examiner's attention: application serial number 10/792,498 and 10/650,591. The Examiner is obviously aware of the existence of these applications as they are used in the above outlined double patenting rejection. The Examiner is invited to consider all past, present, and future prosecution in these co-pending applications.

CONCLUSION

For the foregoing reasons, Applicants respectfully request reconsideration and withdrawal of the pending rejections. Applicants believe that the claims are now in condition for allowance and early notification to this effect is earnestly solicited. Any questions arising from this submission may be directed to the undersigned at (617) 951-7000

Applicant believes no fee is due with this response. However, if a fee is due, please charge our Deposit Account No. 18-1945, under Order No. COTH-P01-001 from which the undersigned is authorized to draw.

Dated: January 11, 2010

Respectfully submitted,

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